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EXAMINER
HUYNH, PHUONG N

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/576,101	Applicant(s) SUHRBIER ET AL.	
	Examiner " Neon" Phuong Huynh	Art Unit 1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. Claims 14-34 are pending.

2. It is noted that new claim 35 is added as indicated in amendment filed 2/20/02. However, no such claim is found in said amendment or the substitute specification. Clarification is required.

3. In view of the amendment filed 2/20/02, the following rejections remain.

4. The drawings, filed 5/22/00, stand not approved. Please see enclosed PTO 948, Notice of Draftsperson's Patent Drawing Review. It is noted that Applicants will forward the corrected drawings at a later time.

5. The disclosure stands objected to because of the following informality: (1) SEQ ID NO: is required on pages 19, line 6, lines 9-10 and lines 14-15.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 14-34 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a recombinant vaccine CTL polyepitope-based composition comprising a polynucleotide encoding CTL epitopes as depicted in Figure 5 derived from pathogens MCMV, influenza, EBV, Adenovirus and EG7 tumor for use as vaccines, does not reasonably provide enablement for vaccine compositions and their use in vaccination against *any* HIV. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) only claims 33 and 34 actually refer to a nucleic vaccine while the other claims refer only to polynucleotides and would appear that the rejection is

inappropriate in relation to claims 14 to 32, (2) the specification is not directed to a vaccine suitable for prevention or treatment of any particular disease but rather describes a general method for formulating a plurality of CTL epitopes so that each CTL epitope can be processed, presented and induces a CTL response subjected to the individual HLA restriction; (3) applicant provides a method for formulating multiple CTL epitopes into an effective vaccine; (4) although it is true that composition claims may be rejected for undue breadth if they read on a significant number of inoperative species, the specification enables the construction and use of a polytope constructs comprising a plurality of CTL epitopes, including those known from any HIV even if a few members of the genus claimed may not prove to be highly effective vaccination agents.

However, the only disclosed use for the claimed polynucleotides in claims 14 to 32 is for a vaccine. A vaccine by definition is for prevention of a particular disease. Given the indefinite number of undisclosed polynucleotide comprising nucleic acid sequence encoding indefinite number of CTL epitopes for any vaccine, there is insufficient guidance and *in vivo* working examples in the specification as filed to demonstrate that said undisclosed polynucleotide would be useful for preventing any undisclosed disease, including the inoperative species of undisclosed species of polynucleotide.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

The specification discloses only a polynucleotide comprising multiple (up to ten) murine CTL epitope as depicted in Figure 5 from pathogens listed in Table 2 on page 14 in which the pathogens are from Epstein Barr Virus, Influenza virus, Cytomegalovirus, and Adenovirus. The response to said CTL epitopes from different pathogens are restricted by individual's HLA class where said CTL epitopes are linked contiguously to a T helper cell epitope from Ovalbumin and a B cell epitope from plasmodium faliciparum in a linear fashion (See Fig 5, in particular) that expressed in vaccinina virus vectors and uses to vaccinate mice against MCMV, influenza, EBV and EG7 tumor.

However, the specification fails to provide guidance as to which polynucleotide encoding which CTL epitopes from HIV that can use in a recombinant nucleic vaccine against HIV infection. The specification does not disclose how using a recombinant vaccinia vector containing a polynucleotide encoding CTL epitopes from Influenza, EBV, Cytomegalovirus, Adenovirus and EG7 tumor can be extrapolated to protect **HIV** infection. Further, there is insufficient evidence that nucleic acid (DNA) vaccine using CTL epitopes from Influenza, EBV, Cytomegalovirus as depicted in Fig. 5 can prevent AIDS and against HIV infection. Applicants have not disclosed *any* "CTL epitopes" from HIV other than **murine** CTL epitopes from Epstein Barr Virus, Influenza Virus, Cytomegalovirus and Adenovirus depicted in Fig. 5 and listed in Table 2, which, in turn, can be used as a vaccine against HIV infection. The claimed invention of "Nucleic acid vaccine" as recited claim 35 against *any* "a plurality of pathogens", including "HIV" is broad and not enabled. Reasonable correlation must exist between the scope of the claims and scope of enablement. The specification has not enabled the breadth of the claimed invention in view of the teachings in the specification as filed. The lack of guidance in the specification as to which CTL epitopes from HIV are appropriate for nucleic acid vaccine against HIV infection is unpredictable and the amount of experimentation required to enable one of skill in the art to practice the claimed invention.

The state of the art is such that even though HIV vaccine research has been under way for 10 years, not a single vaccine has been demonstrated to be effective against AIDS (See page 1993 col. 3, last two paragraph, JAMA 282 (21): 1992-1994; PTO 892). Ramsay *et al* summarizes that "vaccine involving proteins or whole inactivated virions have not, to date, reliably induced either antibodies capable of neutralizing HIV or CTL responses, in human or non-human primates and for reasons which remain unclear, even DNA vaccines do not appear to reliably induce CTL response in outbred primates" including humans (see page 31 column 2, in particular).

In view of the insufficient number of working examples, the lack of guidance in the specification, the breadth of the claims, and the unpredictable state of the art with respect to *in vivo* treatment using any therapeutics, it would require undue experimentation for one skilled in the art to practice the entire **scope** of the claimed invention.

8. Claims 14-34 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that applicants are not required to disclose every species encompassed by their claims even in an unpredictable art and the selection of a particular CTL epitope sequence is not limiting since a large number of CTL epitopes are already known in the literature.

Although some CTL epitopes are already known in the literature at the time the invention as filed, not all CTL epitopes whether it is disclosed or undisclosed are useful for a vaccine for preventing an infinite number of undisclosed disease. The only use for the claimed polynucleotides is for a vaccine. A vaccine by definition is for prevention of a particular disease. Given the indefinite number of undisclosed polynucleotide comprising nucleic acid sequence encoding indefinite number of CTL epitopes for any vaccine, there is insufficient number of species of polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes for a vaccine to describe the genus. Further, there is insufficient written description about the structure associated with function of *any* polynucleotide comprising *any* nucleic acid sequence encoding a plurality of *any* CTL epitopes, *any* nucleic acid sequence encoding *any* CTL epitopes derived from a plurality of *any* pathogens.

The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably convey to the artisan that the inventor had possession at the time of the ...claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 USPQ2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the Applicants had possession at the time of invention of the claimed polynucleotides and the nucleic acid vaccine recited in claims 14-34. The nucleic acid sequences recited in claims 14-34 encompass a large genus of polynucleotides and vaccines. There is insufficient disclosure in the specification to reasonably conveys to the artisan that the inventors had possession of the claimed invention.

Applicant has described only a polynucleotide encoding multiple murine CTL epitopes from murine Cytomegalovirus, lymphocytic choriomenigitis, influenza, EBV, Adenovirus, T

helper cell epitopes from *Berghei circumsporozoite* and Ovalbumin, and B cell epitopes from *plasmodium falciparum* as disclosed in Table 2 expressed in a vaccinia viral vector depicted in Fig. 5. The specification further discloses that the CTL epitopes are arranged in tandem in a contiguous sequence and the said CTL epitopes are from **different** HLA alleles flanking by a B cell epitope from *plasmodium falciparum* (See Fig 5, in particular). The arrangement of the ten CTL epitopes within the construct is such that two CTL epitopes in tandem are from the same MHC class I HLA alleles but from different pathogens (See Figure 5 and Table 2, in particular). The specification as filed does not adequately describe the claimed genus, which encompasses CTL epitopes other than the one depicted in Fig. 5 and listed in Table 2 such that one skilled in the art would conclude that applicants were in possession of the claimed invention.

One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicant was not in possession of the claimed genus. *see University of California v. Eli Lilly and Co. 43 USPQ2d 1398.* In re Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111 indicates that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.). One of ordinary skill in the art would reasonably conclude that the only sequence depicted in Fig. 5 fails to provide a representative number of species to describe the genus as broadly claimed.

9. Claims 14-34 stand rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection** for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that there is clear support for such claims in the specification, such as page 2, line 10-16, page 3, lines 28-29 which provides support for at least ten or more epitopes, page 2 paragraph 14 and page 2 paragraph 6 provides support for a "plurality of epitopes".

However, claims 14-34 as written represent a departure from the specification and the claims as originally filed because the specification on page 2, lines 10-16 (now paragraph 6 of the

substitute specification) and the claims as originally filed require that at least the polynucleotide including at least one sequence encoding a plurality of cytotoxic T lymphocyte epitopes from one or more pathogens and wherein the at least one sequence is "**substantially free of sequences encoding peptide sequences naturally found to flank the CTL epitopes**". Further, the specification and the claims as originally filed do not provide a clear support for at least "**two**" (claims 14-16, 26-34), "**nine**" (claim 18) and "**ten**" (claim 19) CTL epitopes because the range within a range such as the specific "**two**", "**nine**" and "**ten**" epitopes have no support in the specification and the claims as originally filed. Likewise, the "the viral vector" in claim 21 has no support in the specification and the claims as originally filed because the specification on page 3 lines 13-16 discloses the specific vector such as "vaccinia vectors", "avipox virus vectors", "bacterial vectors", "virus-like particles" and "rhabdovirus vectors" but not "the virus vector". Thus, the recitation of "virus vector" in claim 21 represents a departure from the specification and the claims as originally filed because it broadened the claimed vector.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

11. Claims 20-24 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the term "virus-like particle" is well known in the art. However, the phrase "virus-like particle (VLP)" as recited in 21 and 24 is ambiguous. As written, it means viral particles or DNA plasmid from virus found in nature rather than the viral particles produced by vaccinia virus that has been engineered to express the T cell epitopes. One of ordinary skill in the art cannot appraise the metes and bounds of the claimed invention.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claim 15 is rejected under 35 U.S.C. 102(b) as being anticipated by Whitton et al *et al.* (of record, J. Virology 67(1): 348-352, January 1993; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) the present invention is that CTL epitopes can be joined end to end either contiguously or with spacing amino acids not normally associated with those epitopes, (2) Whitton et al provides a construct containing two CTL epitopes each with a start codon and refers to these constructs as "mini-genes" because they each contain their own start codon for initation of translation and (3) as is clear from the present claims, the inclusion of a start codon for every epitope of the present invention is excluded.

However, claim 15 recites a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitope wherein the sequence encoding said epitopes are contiguous.

Whitton *et al.* teach a polynucleotide **comprising** two CTL epitopes (MG3 and MG4) from lymphocytic choriomeningitis virus (LCMV) in an expression vector (VVMG34) wherein said vector is a viral vector from vaccinia virus (See page 349, left column Materials and Methods; page 349 right column, page 350 Fig. 2, in particular). The reference further teaches a nucleic acid comprising said polynucleotide encoding two CTL epitopes in a vaccinia virus vector which is administered to mice (See page 349, col. 1, paragraph 1 and col. 2, paragraph 2 and 3, in particular). Mice inoculated with a single dose of recombinant vaccinia vaccine are protected from a lethal dose of LCMV challenge and this protective effect is dependent upon the appropriate MHC haplotypes as demonstrated by *in vitro* CTL assays and *in vivo* protection assays (See Fig2 and Table 1, in particular). Whitton *et al.* further teach that in order to protect an outbred population such as humans; a vaccine must induce response on most if not all histocompatability complex backgrounds to prevent the risk of vaccine failure due to nonresponder vaccinees. By using the minigene approach, it would be possible to encode up to

50 CTL epitopes in a viral vector, such as vaccinia virus (See page 351, column 1). The reference further teaches how to construct recombinant vaccinia virus carrying a polynucleotide encoding multiple CTL epitopes from peptides as short as 12 amino acid (See page 349, col. 1 Materials and Methods, in particular). The benefits of the combined vaccine confers a level of protection virtually identical to that individual vaccine alone and the protective effects of individual epitope may be enhanced in a combined vaccine (See page 351, left column). Thus, the reference teachings anticipate the claimed invention.

14. Claims 14-16, 20-22, 25, 27 and 33-34 stand rejected under 35 U.S.C. 102(b) as being anticipated by Lawson et al (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1) Lawson et al disclose not two CTL epitopes present in a single construct, but one epitope and the signal sequence from adenovirus E//19K glycoprotein.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one CTL epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous. Thus, the reference teachings anticipate the claimed invention.

15. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

16. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor

and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

17. Claims 14 and 17-19 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Whitton *et al.* (of record, J. Virology 67(1): 348-352, January 1993; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The claimed invention as recited in claims 14, 17-19 differs from the reference only by the recitation of said polynucleotide encoding 3, 9 or 10 CTL epitopes.

Whitton *et al.* teach a polynucleotide **comprising** two CTL epitopes (MG3 and MG4) from lymphocytic choriomeningitis virus (LCMV) in an expression vector (VVMG34) wherein said vector is a viral vector from vaccinia virus (See page 349, left column Materials and Methods; page 349 right column, page 350 Fig. 2, in particular). The reference further teaches a nucleic acid comprising said polynucleotide encoding two CTL epitopes in a vaccinia virus vector which is administered to mice (See page 349, col. 1, paragraph 1 and col. 2, paragraph 2 and 3, in particular). Mice inoculated with a single dose of recombinant vaccinia vaccine are protected from a lethal dose of LCMV challenge and this protective effect is dependent upon the appropriate MHC haplotypes as demonstrated by *in vitro* CTL assays and *in vivo* protection assays (See Fig2 and Table 1, in particular). Whitton *et al.* further teach that in order to protect an outbred population such as humans; a vaccine must induce response on most if not all histocompatability complex backgrounds to prevent the risk of vaccine failure due to nonresponder vaccinees. By using the minigene approach, it would be possible to encode up to

50 CTL epitopes in a viral vector, such as vaccinia virus (See page 351, column 1). The reference further teaches how to construct recombinant vaccinia virus carrying a polynucleotide encoding multiple CTL epitopes from peptides as short as 12 amino acid (See page 349, col. 1 Materials and Methods, in particular). The benefits of the combined vaccine confers a level of protection virtually identical to that individual vaccine alone and the protective effects of individual epitope may be enhanced in a combined vaccine (See page 351, left column). Whitton *et al* teach that the protective effects of individual epitopes may by synergistic and the combination vaccine confers a level of protection virtually identical to that by individual epitope alone (See Whitton et al, page 351, left column 1, in particular). From the teaching of Whitton as discussed supra, it is apparent that one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success in producing the claimed invention because Whitton *et al* teach that polynucleotide can encode up to 50 CTL epitopes (See page 351, column 1).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to add additional CTL epitopes as taught by Whitton et al to the contiguous CTL epitopes as taught by Lawson et al.

One having ordinary skill in the art would have been motivated to prepare recombinant vaccinia vaccine containing 3, 9 and 10 CTL epitopes because the benefit of having multiple CTL epitopes in a single vaccine would improve vaccine coverage in a population having heterogeneous MHC genetic backgrounds as taught by Whitton *et al*.

18. Claims 14 and 26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) and Whitton *et al.* (of record, J. Virology 67(1): 348-352, January 1993; PTO 892) in view of Berzofsky *et al.* (of record, U.S. Patent No. 5,980,899; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that (1)) Lawson et al disclose not two CTL epitopes present in a single construct, but one epitope and the signal sequence from adenovirus E//19K glycoprotein.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen

is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson et al and Whitton et al have been discussed supra.

The claimed invention in claim 26 differs from the references only by reciting polynucleotide encodes CTL epitopes from a plurality of pathogens.

Berzofsky *et al* teach recombinant vaccinia virus expressing a polynucleotide encoding cytotoxic T cell (CTL) epitopes from hepatitis C virus NS5, vSC8, vSC25 and HIV-1gp 160 (See column 18, line 39; column 19, line 29 in particular) and chronic infection is of medically important problem (see column 1 line 65 bridging column 2, line 10).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to make and use CTL epitopes from multiple pathogens as taught by Berzofsky *et al* for a recombinant combination vaccine as taught by Lawson *et al.* From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One of ordinary skill in the art at the time the invention was made would have been motivated to use CTL epitopes from multiple pathogens taught by Berzofsky for a recombinant combination vaccine as taught by Lawson *et al* because the protective effects of individual epitopes may by synergistic and the combination vaccine confers a level of protection virtually identical to that by individual epitope alone as taught by Whitton et al (See Whitton et al, page 351, left column 1, in particular).

19. Claims 14, 25 and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (J Virology 68(6): 3505-3511, June 1994, PTO 892, see entire document) in view of Del Val *et al* (of record, J. Virology 65(7): 3641-3646, July 1991; PTO 892) or Latron *et al* (of record, Proc. Natl. Acad. Sci. USA 88: 11325-11329, Dec 1991; PTO 892) or Burrows *et al* (of record, J. General Virology 75: 2489-2493, 1994; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full

length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson et al have been discussed supra.

The claimed invention as recited in claims 14, 17-19 differs from the references only by the recitation of said polynucleotide encoding 3, 9 or 10 CTL epitopes.

The reference teachings differ from the claimed invention by not using CTL epitopes from cytomegalovirus or influenza virus or Epstein-Barr virus.

Del Val *et al* teach CTL epitopes from cytomegalovirus and a recombinant vaccine against lethal CMV infection (See page 3641, Materials and Methods; page 3643, Fig. 2, in particular).

Latron *et al* teach CTL epitopes from Influenza by site-directed mutagenesis of genomic DNA (See page 11325, Materials and Methods; page 11326, Table 1, in particular). Latron *et al* further teach that mutation in the amino residues at 114 and 116 can abolish CTL immune response against Influenza (See Table 1, in particular).

Burrows *et al.* teach five new CTL epitopes of Epstein-Barr virus (See table 1, in particular) and EBV infection appears to be common in Western societies and there is appears to be 50% chance of developing infectious mononucleosis (See page 2489, column 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the CTL epitopes from cytomegalovirus as taught by Del Val *et al* or the CTL epitope from Influenza as taught by Latron *et al* or the CTL epitopes of Epstein-Barr virus as taught by Burrows *et al* with the CTL epitope from LCMV as taught by Whitton *et al* or the CTL epitope as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to substitute the CTL epitopes from CTL epitope from Influenza taught by Lawson *et al* with the CTL epitopes from CMV taught by Del Val *et al* or CTL epitopes from Influenza taught by Latron *et al* or CTL epitopes of Epstein-Barr virus taught by Burrows *et al* for a vaccine comprises CTL epitopes from a pathogen for a vaccine taught by Lawson *et al* with the expectation that the vaccine using CTL epitopes from the CTL epitope from Influenza taught by Lawson *et al* would also have the same protective effect when substitute CTL epitopes from other pathogens such as cytomegalovirus, Influenza or Epstein-Barr virus.

20. Claims 14, 20-21 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Panicali *et al* (of record, U.S. Pat No. 5,656,465, filing date May 4, 1994; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention in claims 14, 20-21 and 23 differs from the references only by the recitation of avipox viral vector.

Panicali *et al* teach a method of in vivo gene delivery using viral vector including, avipox (e.g. fowl pox) for delivering a wide range of genetic material (polynucleotide) (See column 3, line 21; column 7, line 3; column 11 line 17, in particular) that encode cytokines for tumor therapy (See column 4, line 28; column 5 line 31, in particular). Panicali *et al* further teach that fowl pox viruses produces abortive infection in humans and therefore do not cause disease and it can be readily be used to deliver a wide range of genetic material including multiple genes (see column 3, line 40, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the vaccinia vector as taught by Lawson *et al* with the avipox virus vector as taught by Panicali *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to use avipos vector to deliver polynucleotide vaccine because the advantages of using avipox is that these viruses produce abortive infection in humans and therefore do not cause

disease and they can be readily be used to deliver a wide range of genetic material including multiple genes as taught by Panicali *et al* (See column 3, line 41).

21. Claims 14, 20-21, 24, and 29-31 are rejected under 35 U.S.C. 103(a) as being unpatentable Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Adams *et al* (of record, Intern. Rev. Immunol 11: 133-141, 1994; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention in claims 14, 20-21, 24 differs from Lawson *et al* only by the recitation of vector wherein the vector is a virus-like particle (VLP) and the polynucleotide comprising a nucleic acid sequence encoding T and B cell epitopes as recited in Claims 29-31.

Adams *et al* teach that in order to develop vaccines that are more immunogenic than simple monomeric antigen vaccine, a polynucleotide encoding CTL epitopes to include multiple copies of T-cell and B-cell epitopes expressed in a virus-like particle (VLP) vector would enhance immune response (See page 133, Abstract, in particular). Adams *et al* further teach that VLP vector can include nucleic acid encoding polypeptide up to 43 kDa in size (See page 140, in particular).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to substitute the vaccinia virus vector as taught by Lawson *et al* with the VLP viral expression vector comprising a polynucleotide encoding CTL epitopes and T helper cell and B cell epitopes as taught by Adams *et al* to enhance CTL response. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having

ordinary skill in the art would have been motivated to make a polynucleotide encoding CTL epitopes to include T helper cell and B cell epitopes because T helper cell would enhance cytokine production while B cell epitopes would induce humoral immune response along with potent CTL immune response in the absence of adjuvant. One having ordinary skill in the art would substitute the vaccinia vector as taught by Lawson *et al* with the VLP vector as taught by Adams because its versatility in packing nucleic acid encoding polypeptide up to 43 kDa in size (See page 140, in particular).

22. Claims 14 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Celis *et al* (of record, Proc. Natl. Acad. Sci USA 91: 2105-2109, March 1994; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention recited in claims 14 and 28 differs from the references teachings only by the recitation of CTL epitope from tumor.

Celis *et al* teach immunotherapy for melanoma using CTL epitopes from tumor such as MAGE-1, MAGE-2, and MAGE from melanoma for cancer vaccine (See abstract and Table 1; page 2109, last paragraph, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to reverse transcribe the CTL epitopes from tumor as taught by Celis *et al* before substitute with the polynucleotide encoding the CTL epitope from Influenza as taught by Lawson *et al* for a cancer vaccine. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in

producing the claimed invention. One having ordinary skill in the art would have been motivated to use tumor epitopes as taught by Celis *et al* for a cancer vaccine using the approach as taught by whitton which would prevent the risk of vaccine failure due to nonresponder vaccinees.

23. Claims 14 and 29-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Widmann *et al* (of record, J Immunol Method 155: 95-99, 1992; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention recited in claims 14 and 29-30 differs from the references teachings only by the recitation of said polynucleotide encoding CTL epitopes, including T helper cell epitope.

Widmann *et al* teach T helper cell epitopes from *P. berghei* and *Plasmodium yoelii* (see page 96, col. 1, paragraph 1 and page 97, col. 2, paragraph 1, in particular) are linked to the CTL epitope (DSYIPSAEKI) in tandem in order to enhance the cytotoxic response of mice (See page 96, col. 2 Results and Discussion, page 97 col. 2, paragraph 1, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to reverse transcribe the T helper epitopes as taught by Widmann *et al* before linking the polynucleotide encoding said T helper epitopes to the polynucleotide encoding the CTL epitope from Influenza virus as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to make polynucleotide encoding CTL epitopes together with T

helper cell epitopes because T helper cell epitope has been shown to enhance the CTL as taught by Widmann *et al*.

24. Claims 14, 29 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Potter *et al* (of record, U.S. Patent No. 5,708,155; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention recited in claims 14, 29 and 32 differs from the references teachings only by the recitation of said polynucleotide encoding CTL epitopes, including toxin.

Potter et al teach that in order to increase the immunogenicity of the antigen, a DNA encoding a leukotoxin polypeptide can be fused to a selected antigen (See Abstract, in particular). The reference further teaches that leukotoxin as a carrier in a vaccine can enhance immune response of the antigens.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare a polynucleotide comprising nucleic acid sequence encoding a toxin as taught by Potter and CTL epitopes for a vaccine as taught by Lawson *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. One having ordinary skill in the art would have been motivated to make nucleic vaccine comprising a polynucleotide encoding CTL epitopes and toxin because the use of toxin as an adjuvant taught by Potter et al can improve the immune response of any vaccine such as the ones taught by Lawson *et al*.

25. Claims 14 and 29-32 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Lawson *et al* (of record, J Virology 68(6): 3505-3511, June 1994, PTO 892) in view of Adams *et al* (of record, Intern. Rev. Immunol 11: 133-141, 1994; PTO 892) or Potter *et al* (of record, U.S. Patent No. 5,708,155; PTO 892) or Widmann *et al* (of record, J Immunol Method 155: 95-99, 1992; PTO 892) for the same reasons set forth in Paper No 9.

Applicants' arguments filed 2/20/02 have been fully considered but are not found persuasive.

Applicants' position is that Whitton et al or Lawson references alone or in combination are sufficient to render the present invention unpatentable.

However, Lawson *et al* teach recombinant vaccinia virus as an expression vector expressing the full-length polynucleotide of HA containing at least one CTL epitope (the full length inherently contains more than one epitope) derived from a pathogen wherein the pathogen is **influenza** virus and Adenovirus (leader sequence) (See page 3506, Materials and methods, in particular). The said epitopes are contiguous.

The teachings of Lawson *et al* have been discussed supra.

The claimed invention recited in claims 14 and 29-32 differs from the reference teachings only by the recitation of said polynucleotide encoding CTL epitopes, including T helper cell epitope, B cell epitope or Toxin.

Adams *et al* teach that in order to develop vaccines that are more immunogenic than simple monomeric antigen vaccine, a polynucleotide encoding CTL epitopes to include multiple copies of T-cell and B-cell epitopes expressed in a virus-like particle (VLP) vector would enhance immune response (See page 133, Abstract, in particular).

Widmann *et al* teach T helper cell epitopes from *P. berghei* and *Plasmodium yoelii* (see page 96, col. 1, paragraph 1 and page 97, col. 2, paragraph 1, in particular) are linked to the CTL epitope (DSYIPSAEKI) in tandem in order to enhance the cytotoxic response of mice (See page 96, col. 2 Results and Discussion, page 97 col. 2, paragraph 1, in particular).

Potter *et al* teach that in order to increase the immunogenicity of the antigen, a DNA encoding a leukotoxin polypeptide can be fused to a selected antigen (See Abstract, in particular). The reference further teaches that leukotoxin as a carrier in a vaccine can enhance immune response of the antigens.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to reverse transcribe the T helper epitopes as taught by Widmann *et al* before

fusing it the polynucleotide encoding the CTL epitope from Influenza virus as taught by Lawson *et al* together with the T helper cell epitopes as taught by Widmann or the T-cell and B-cell epitopes as taught by Adams *et al* or leukotoxin as taught by Potter *et al*. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to make a polynucleotide encoding CTL epitopes to include T helper cell and B cell epitopes because T helper cell would enhance cytokine production while B cell epitopes would induce humoral immune response along with potent CTL immune response in the absence of adjuvant as taught by Adams *et al.* Widmann *et al* teach T helper cell epitope has been shown to enhance the CTL as taught by Widmann *et al*.

26. The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timeless extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cirri. 1993); *In re Long*, 759 F.2d 887, 225 USPQ 645 (Fed. Cirri. 1985); *In re Van Onramp*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

27. Claims 14-34 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 14-35 of USSN 09/957,107 for the same reasons set forth in Paper No 9.

(1) Claim 14 of USSN 09576,107 recites a polynucleotide comprising a nucleic acid sequences encoding at least two CTL epitopes wherein at least two of the epitopes are restricted by the same HLA gene. Therefore, claim 14 of USSN 09576,107 is included in the instant claims

14-15 which drawn to a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes, wherein at least two of the sequences encoding said CTL epitopes are contiguous or spaced apart by intervening sequence do not (i) comprise methionine or (ii) encode naturally occurring flanking sequences of the epitopes as recited in claim 14 of instant application. Note, although Claim 14 of USSN 09576,107 does not explicitly claim the CTL epitopes are contiguous or spaced apart and claim 14 of instant application does not explicitly claim the said epitopes are restricted by the same HLA gene, since all CTL epitopes are from MHC class I, the spacing between epitopes is an obvious variation of the recombinant fusion protein. Further, the recitation of "at least two CTL epitopes" in claim 14 of USSN 09576,107 is an obvious variation of "a plurality of CTL epitopes" as recited in instant claim 14.

(2) Claims 15-34 of USSN 09576,107 are the same as that recited in the instant claims 15-32.

(3) Claim 35 of USSN 09576,107 recites a nucleic vaccine comprising a polynucleotide comprising a nucleic acid sequence encoding at least two CTL epitopes from one or more pathogens, wherein at least two of said epitopes are restricted by the same HLA gene and an acceptable carrier which is included in the claims 33 and 34 of instant application since claim 33 of instant application recites a nucleic acid vaccine comprising a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes, wherein at least two of said CTL epitopes are contiguous or spaced apart by intervening sequences, wherein said intervening sequences do not (i) comprise an initiation codon or (ii) encode naturally occurring flanking sequences of the epitopes, and an acceptable carrier and claim 34 of instant application recites a nucleic acid vaccine comprising a polynucleotide comprising a nucleic acid sequence encoding a plurality of CTL epitopes, wherein the sequences encoding said CTL epitopes are contiguous and an acceptable carrier. Since the claims of instant application include the invention of USSN 09576,107, issuance of a patent to the instant application would improperly extend the right to exclusivity. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

28. No claim is allowed.

29. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for response to this final action is set to expire THREE MONTHS from the date of this action. In the event a first response is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event will the statutory period for response expire later than SIX MONTHS from the date of this final action.

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to "Neon" Phuong Huynh whose telephone number is (703) 308-4844. The examiner can normally be reached Monday through Friday from 9:00 am to 6:00 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (703) 308-3973. Any inquiry of a general nature or relating to the status of this application should be directed to the Technology Center 1600 receptionist whose telephone number is (703) 308-0196.

31. Papers related to this application may be submitted to Technology Center 1600 by facsimile transmission. Papers should be faxed to Technology Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-7401.

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May 20, 2002

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